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AND THE SCIENCES SUPPORTING PUBLIC HEALTH

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EDITORIAL

THE ENGLISH EXPERIMENT

AFTER long debate and not without some trepidation, organized pharmacy and medicine became part of a nationalized health program in England on July 5th. This was a momentous day in the annals of medicine and pharmacy, whether the outcome shall be good or bad. No one, regardless of his personal feelings on the matter, can be certain of the eventual result.

From now on all people of the British Isles, disregarding their economic or social status, are entitled to a complete program of medical care including medical and surgical attention, drugs and appliances. All this is provided without cost except through taxation.

If this had happened in any other country except England it would not be so significant but England is the cradle, so to speak, of human liberty and freedom. That this has come to pass there causes one to reflect on the possibilities of its outcome. It is quite apparent, even to foreign onlookers, that the labor government in England is making a conscientious effort to bring their country out of the economic morass into which it descended during the war. The war cost England more than we Americans realize and the low standard of living which the English have endured uncomplainingly for the past few years would have caused open revolt in the United States in one week. It is not so apparent whether the labor government will succeed in bringing England into an era of prosperity nor is it encouraging to those, who love liberty above all, to see the continued encroachment of individual rights there with the purported justification that it is for the common good.

The new National Health Service plan is relatively simple in its concept. From now on all physicians and pharmacists are in essence almost civil servants; their charges are established and paid for by the state. Although private patients are permitted, few indeed will choose to pay for medical care when it is already presumably available and paid for through taxation. Many more individuals are likely to seek medical attention than have done so in the past since it

is free. Actually the ranks of those needing medical attention will be cluttered with those who need none at all, being there only through whimsy or the desire to get full return on their tax investment. More prescriptions will be written and filled and physicians and pharmacists will be busier than ever; but from here on we are faced with a great unknown. As the pressure on the medical and pharmaceutical profession increases as will the overall cost to the state what will result? Will patients get the same careful examination and diagnosis? Will prescriptions be filled as meticulously? Will the state continue to approve the use of expensive drugs or adopt a drug table of cheaper products? In providing more care will not the finest medical care as known today be scaled down to a very average quality? Will the search for new drugs be pressed as diligently when the use of some new discovery is not likely to profit the company developing it? Will individual initiative drop to the low level that is almost the rule in most government agencies with which we have had experience? These are the questions that should worry us for upon their answers depends much.

There are two schools of thought on these questions as with all such matters that stem from the current competition between the state *vs.* the individual in guiding the affairs and lives of men. Those who believe in more and more regimentation and control argue that no individual is best off following his own inclinations; that everything should be prescribed for him by the state. It is the opinion of these well-meaning individuals that nothing is more important to man's happiness than security and that everything must be done for him by the state so as to put his mind at ease. His whole life is bit by bit pre-arranged and ordained; he lives in perfect security albeit in complete boredom. Gradually, however, as those who supervise penal institutions can attest, a man living such a secure life becomes an automaton; working, living, sleeping in an orderly fashion but gradually losing his creative instincts and his drive until he is little different than the horse or the ox that works in the field. Once this mental inertia is fully developed it is permanent.

Man has risen above other animals because he has had the capacity to meet the challenge of nature and the competition offered by other animals both more numerous and more powerful. Throughout history it has not been adversity which destroyed certain civilizations but over refinement and ease until the people were unable to

meet the competition offered by those having far less excepting the will to live and conquer.

On the surface free medical care, like all forms of security offered by the state, seems a great boon to the people. So are these things insofar as the immediate future is concerned. But suppose this security leads to a loss of personal freedom and a lack of initiative accompanied by complacency with things as they are. We may then expect to see future progress curtailed. A civilization may yet develop like that illustrated by an ant colony. This is one of the oldest, unchanging and most efficient organizations in all of nature, but what a life to lead!

There are still a few people left in the world who consider freedom the most precious possession of man, a possession not to be surrendered for security regardless. These same few believe also that great joy can only be bought by meeting the challenge of adversity and hardship. Possibly a new race of men may be in the making wherein such thoughts are held ridiculous. If so it would be interesting to know what animals will succed us some few million years hence, exhibiting in museums our fossilized skeletons as animals which once inhabited earth but succumbed through some weakness of unknown origin.

L. F. Tice.

A NEW APPROACH TO TABLET DISINTEGRATION TESTING

By V. M. Filleborn,* Master of Pharm. (Warsaw), M. P. S. (Gr. Britain)

History

THE study of the disintegration of tablets is not new; but in all Pharmacopoeiae with the exception of those of Switzerland and Great Britain, no method is given for testing the disintegration of tablets and there is no universal standard method available for such testing.

Chronological investigation of the literature concerning this subject revealed that in 1930, the American Pharmaceutical Manufacturers' Association Conference discussed this matter for the first time (1). In 1934, The Swiss Pharmacopoeia gave the first published method (2), and in 1936 the subject was discussed at the British Pharmaceutical Conference (1).

In 1939, Brown devised his own method (3), and in the same year the British Pharmacopoeia Committee requested Prof. F. R. Berry to investigate the various methods for testing the disintegration of tablets, and his report was published in 1939 (4).

In 1943, Abbot and Allport published a new method for testing the disintegration of coated pills (5). In July 1944, Berry published a minor improvement to his method of testing the disintegration of tablets (6).

In 1943, J. Thomann also described his own method of testing the disintegration of tablets (7).

In an article published in 1945, F. Bandelin gave a description of a method used in the U. S. A. and known as the method of the American Pharmaceutical Association (8). In a study published in 1945 in Industrial and Engineering Chemistry (Analytical Edition), under the title: "Study of methods for determining availability of vitamins in pharmaceutical products" we can find a method described as a "disintegration test for vitamin tablets" given by U. S. A. War Food Administration (Form SCB-50) (9 & 10).

Several other articles published from 1942 to 1945 by American and British authors (Malpass (11), Calamari and Roth (12),

* Petersen, Ltd., Manufact. Chemists, 3-22, Barrack Str., Cape Town, Union of South Africa.

Hoehn (13), A. Nutter Smith (14), H. Hoyle (15), H. P. Prance, D. Stephenson and A. Taylor (15)) contain descriptions of different individual methods and results of tablet disintegration tests.

Finally in 1945 the 7th Addendum to The British Pharmacopoeia (1932) was published, introducing a new standard test for disintegration of tablets (16).

All these methods described depend only upon physical or chemical testing, and they vary considerably. None of them give a picture of the actual environment of a tablet when swallowed, nor do they give a standard rate of disintegration for different tablets. The majority of them are suited only for production testing and not for laboratory investigation.

General Description of the New Method

The two most important qualities a tablet must possess are:

(a) sufficient mechanical hardness to prevent breakage in packing and transporting,

(b) the ability to disintegrate readily in the stomach, when swallowed.

This investigation is concerned mostly with the latter property of tablets, i. e. to determine primarily in what time a tablet will disintegrate in conditions simulating as accurately as possible the conditions in a normal human alimentary tract.

It is known that in carrying out laboratory investigations "in vitro", we must create conditions as similar as possible to the conditions "in vivo". For this purpose, a new apparatus was devised, as those described by all other authors were not considered satisfactory.

For comparative purposes all the experiments with different tablets were carried out by the following three methods:

(A) Swiss Pharmacopoeia method,

(B) British Pharmacopoeia, 7th Addendum,

(C) Method described below as test in an "artificial stomach".

Finally the results obtained by the test in the "artificial stomach" were controlled by a test "in vivo" by means of using radio-opaque tablets.

As the digestive systems of suitable experimental animals are entirely different from humans, it is not possible to carry out disintegration tests "in vivo" with animals, which would be in any way analogous to disintegration in the human stomach. The only possible study of disintegration in the human alimentary tract is by radiography of radio-opaque tablets. Unfortunately, the tablets usually under test are not radio-opaque, so the only way of testing such a tablet is to create an apparatus giving the conditions of disintegration as similar as possible to the normal human stomach, proceed with the test in such conditions, and afterwards, in testing a batch of radio-opaque tablets in the same apparatus, and "in vivo" in a human stomach, compare the obtained results.

The physiological conditions in which a tablet disintegrates in a normal human alimentary tract consist of:

(a) amount and quality of saliva in the mouth, and time of swallowing,

(b) the volume of gastric juice present,

(c) its acidity,

(d) the amount of peristaltic movements present,

(e) the hydrostatic pressure present during peristalsis.

All these conditions vary considerably in humans; those conditions described by Lovatt Evans (17) and P. B. Hawk (18) and collaborators have been taken as representing, as nearly as possible, the average. Conditions present in various pathological states are too varied to be considered in such an investigation as this.

In carrying out these investigations it was also necessary to consider the various methods of administering tablets. Though various practical methods are in common use, such as crushed tablet swallowed with liquid, or the tablet crushed in the mouth, followed with a draught of liquid, etc., it was thought necessary to investigate the disintegration under the most unfavorable conditions, i. e., a whole tablet swallowed without a preliminary crushing or breaking. It was also considered necessary to treat tablets in a "saliva bath" during the time approximately corresponding to the time of swallowing action, i. e. during which the tablet passes the period of salivary digestion, before testing their disintegration in the new apparatus.

Apparatus and Reagents

The apparatus used—"the artificial stomach"—is described in detail in Figures Nos. 1, 2, 3, and 4.

It consists of a glass vessel (F) which contains 150 mls. of artificial gastric juice at pH of 1.4, for an empty stomach, and pH 3.6-4.0, for a full stomach. The gastric juice (K) is agitated over a height of 0 to 10 cm. above the plastic perforated container (G), by means of a small respiratory pump (P), at the rate 4-5 movements per minute. The whole is contained in a thermostatically controlled water bath (A) at 37° C.

150 mls. of artificial gastric juice represent the normal volume of an empty stomach; the rate of peristaltic contractions is about 4-5 per minute. The height of liquid in the chamber (F) adjusted to rise and fall 10 cm., represents the hydrostatic pressure present in the stomach, and the movement of the juice simulated the agitation of peristalsis in the stomach.

Secretion of fresh gastric juice was allowed for by a dripfeed (I) (J), at a rate of 40 mls./hr., given by Pawlow (17) as the normal secretory rate in the human stomach.

The excess of the gastric fluid, which after several minutes can occur in the testing vessel (F) is collected, during the movement of the fluid in the vessel when it reaches the highest level in the collecting tube (H). This represents the periodical emptying of the stomach into the small intestine and the duodenum.

Salivary digestion is represented by immersing the tested tablet in a vessel containing 2 mls. of artificial saliva, Drawing No. 4—(SB).

The composition of the artificial gastric juice was adopted according to the formula given by Abbot and Allport (5), but improved by adding Gastric Mucin and adjusting the pH to 1.4.

Sodium Chloride	1.4	gm.
Potassium Chloride	0.5	gm.
Calcium Chloride (Hydr.)	0.12	gm.
Gastric Mucin	1.3	gm.
Pepsin B. P. plv.	3.2	gm.
Hydrochloric Acid N/1	approx. 45-50	mls.
Distilled water, to make	1000	mls.

pH = 1.4 (± 0.1)

This formula represents approximately the composition of the gastric contents of an empty stomach.

To imitate the contents of a full stomach, the following formula was used:

A. Sodium Chloride	1.4	gm.
Potassium Chloride	0.5	gm.
Calcium Chloride (Hydr.)	0.12	gm.
Gastric Mucin	1.3	gm.
Pepsin B. P. plv.	3.2	gm.
Hydrochloric Acid N/1	approx. 10-15	mls.
Distilled water, to make	500	mls.
B. Mucilage Gum Acacia	300	mls.
Distilled water, to make	500	mls.

Mixtures A and B were mixed in equal quantities and the pH adjusted to 4 ($\pm$ 0.5).

The Gum Acacia Mucilage was prepared by dissolving 120 gm. Gum Acacia and 0.1 gm. of Phenol (for preservation) in 180 mls. of distilled water.

During the tests in which the content of a full stomach was used, some small pieces (5 to 6) of sterilized sponge (each about twice the size of a tablet) were added to imitate the presence of food in the stomach.

In the first stage of experiments including salivary digestion, a normal human saliva was used; but later it was found necessary, for stabilizing the experiments, to use an "artificial saliva" (as the consistency, composition and pH of different human saliva and in different stages of daily life are changeable) for which a special formula was suggested and adopted according to Starling (17) and Hawk (18).

The differences between disintegration times of various tablets tested in the "artificial stomach," without a saliva bath, with a human saliva bath, and in an artificial saliva bath are shown on Table No. 4.

The composition of the artificial saliva used was as follows:

Calcium Chloride	0.06	gm.
Sodium Chloride	0.45	gm.
Sodium Phosphate Cryst.	0.175	gm.
Calcium Carbonate Light B. P.	1.00	gm.
Gastric Mucin	2.5	gm.
Taka-Diastase Standardized	16.00	gm.
Cholesterol	0.06	gm.
Distilled Water, to make	1000	mls.

The pH of normal human saliva varies between 6.0-7.9; the pH of the artificial saliva was adjusted to 6.7 ($\pm$ 0.5).

Amylase content—100 units/cc. After preparation of artificial saliva this should be tested for Amylase activity according to Hawk (18).

One unit of Amylase may be considered as the amount required to digest 5 cc. of 1% Soluble Starch to the achromic point in 10 min., under the conditions of the test. The number of units of Amylase in 1 cc. of the artificial saliva tested will equal 10 over the number of minutes to the achromic point times 100 (or whatever the dilution of the original saliva might be). From 100 to 150 units are frequently found.

Operation

When the temperature of the water bath has been adjusted and controlled, 150 mls. of artificial gastric juice are placed in the vessel (F), which is then connected by the tube (L) to the respiration pump (P). With the compression valve (Z) open, the empty plastic tablet container (basket) (G) is lowered into the vessel, and by adjusting the throw of the pump and the compression valve, the movement of the gastric juice is controlled to rise and fall 10 cm. The drip-feed reservoir (I) (J) is then filled with gastric juice. When the liquid in the vessel (F) has reached the temperature of the water bath (36.9°-37°C.) a previously weighed tablet is placed in a small dish containing 2 mls. of artificial saliva for 15 sec., and immediately afterwards placed in the plastic tablet container (G) and lowered into the vessel (F) and the time noted. The drip-feed

(I) (J) tap is then opened allowing the passage of 40 mls. of gastric juice per hour, (approx. 10 drops per minute).

The time for disintegration was taken as the time necessary for the tablet to disintegrate into sufficiently small particles to pass through the holes (1/16") of the plastic tablet basket.

Fresh artificial saliva and stomach juice were used for each tablet. The formulæ for an empty stomach were used in testing tablets which are usually taken on an empty stomach, or 4 hours after meals. The formulæ for a full stomach were used in testing tablets which are taken with, or immediately after meals.

Experimental

The tablets tested in this study consisted of: Phenobarbitone gr. ¼ and ½, Ephedrine Hydrochloride gr. ½ and 1, Mepacrine Hydrochloride 0.1 gm., Sulfathiazole 0.5 gm., Sulfapyridine 0.5 gm., Sulfanilamide 0.5 gm. and Sulfadiazine 0.5 gm.

They were taken from various batches, manufactured by British, American, French, Swiss and South African manufacturers.

For each experiment one lot of 75 tablets of the same batch and the same manufacturer was used.

From the lot of 75 tablets, 25 tablets were separately tested according to the Swiss Pharmacopeia method, 25 according to the B. P. 7th Addendum test, and finally 25 in the "artificial stomach."

The results of the three different tests were added, (25 results in each test) and an average time was calculated.

The same method was applied to the average weight and resistance of tablets.

The resistance of tablets under test was measured by a special apparatus (French origin) which gives the resistance of tablets to piercing, and the pressure exerted upon the tablet by this apparatus is calculated in terms of Kilograms per sq. centimetre.

Since the tablets tested for resistance (hardness) by this apparatus are broken during testing, a special lot of 75 tablets of each batch was tested, before each experiment for disintegration, and the average hardness calculated.

From Table No. 1 it is easy to observe that there is no relationship between the times of disintegration obtained by the Swiss Pharmacopoeia or B. P. 7th Addendum methods, and the test by the "artificial stomach."

Generally speaking the times resulting from the Swiss and British tests are much shorter than the times in the "artificial stomach."

After having completed these experiments with non radio-opaque tablets, four different batches of radio-opaque tablets were tested in the "artificial stomach" and the results are given in Table No. 2. For complete confirmation of these experiments an "in vivo" test was undertaken. 15 radio-opaque tablets from the same batches as previously tested "in vitro" were tested "in vivo" on 3 different subjects during a period of 4 days under frequent radiographic observation. The results are given on Table No. 3.

A series of experiments was also undertaken to find any relationship existing between the hardness of tablets and the time of disintegration.

For this purpose two kinds of granules ready for tableting were chosen: Sulfanilamide Batches Nos. 2002 and 2003 and Sulfadiazine Batch No. 3001.

Both were tableted on the same machine, (Rotary Stokes B. 2). During the tableting process the pressures exerted on the punches were measured and increased twice in each case (a total of three different pressures in each case). From each run of tablets on the machine, with different pressures, 100 tablets were taken as a sample, from which 75 were weighed to find the average weight, and 25 were tested for resistance, (hardness).

All of the 75 tablets (which were weighed) were tested for disintegration in the "artificial stomach," and the average time of disintegration calculated.

Summary

The need for new methods of the determination of tablet disintegration in pharmaceutical research, particularly when these products are administered intact, has recently been emphasized. Simple "in vitro" disintegration tests have proved to be only of limited value and may even lead to misinterpretation. The only suitable procedure for determining the disintegration of tablets is that based on comparing results of the "in vitro" test with those of the test "in vivo." It has been demonstrated that the above described method known as the test in "artificial stomach" is one which shows results nearest to the times of disintegration "in vivo." The precision of the

assays are superior to those of the British and Swiss Pharmacopoeias as they show a definite relationship between the tests "in vivo" and "in vitro."

Secondly the experiments with the disintegration of tablets in "artificial stomach" also show certain relationships between the hardness of tablets and the times of disintegration, (Table 5 and the graphical representations: 1, 2 and 3) which could be mathematically defined once further research has been conducted with varying types and larger quantities of tablets.

Since the results obtained from the method of the Swiss Pharmacopoeia seldom correlate with those obtained by the British Pharmacopoeia method, and neither represent an imitation of the environment of a tablet after swallowing, it is suggested that the "artificial stomach" method, or a simplification of this would be a more valid test for the disintegration of a tablet.

TABLE NO. 1

Experiment No.	Manufacturer	Batch No.	Average weight of one tablet in gm. in each Batch	Average resistance (hardness) of 75 tablets in Kgm/sq. c. in each Batch	Test Results: Method A (Swiss Pharmacopoeia) Average time of disintegration	Method B (B. P. 7th Add.) Average time of disintegration	Method C ("artificial stomach") Average time of disintegration
				Phenobarbitone Gr. ¼ Tablets			
1	L	201	0.0271	60	1 min. 02 sec.	0 min. 52 sec.	2 min. 03 sec.
2	M	301	0.0285	65	0 min. 53 sec.	0 min. 25 sec.	1 min. 57 sec.
				Phenobarbitone Gr. ½ Tablets			
3	L	401	0.0558	115	1 min. 03 sec.	0 min. 43 sec.	2 min. 15 sec.
4	M	501	0.056	119	1 min. 32 sec.	0 min. 57 sec.	4 min. 01 sec.
				Ephedrine Hydrochloride Gr. ½ Tablets			
5	P	601	0.0362	57	1 min. 42 sec.	1 min. 08 sec.	9 min. 17 sec.
6	R	701	0.0364	90	3 min. 04 sec.	2 min. 28 sec.	11 min. 39 sec.
				Ephedrine Hydrochloride Gr. 1 Tablets			
7	P	801	0.071	129	0 min. 59 sec.	1 min. 12 sec.	5 min. 51 sec.
8	R	901	0.0854	167	4 min. 19 sec.	3 min. 08 sec.	12 min. 05 sec.
				Sulfathiazole 0.5 gm. Tablets			
9	H	81	0.6475	737	0 min. 48 sec.	1 min. 27 sec.	2 min. 01 sec.
10	F	61	0.5597	175	0 min. 38 sec.	0 min. 35 sec.	14 min. 09 sec.
11	F	62	0.5757	175	0 min. 23 sec.	0 min. 34 sec.	1 min. 58 sec.
12	F	63	0.5592	500	1 min. 13 sec.	1 min. 27 sec.	2 min. 00 sec.
13	F	64	0.538	733	0 min. 52 sec.	0 min. 56 sec.	2 min. 03 sec.
14	G	71	0.5788	460	0 min. 38 sec.	0 min. 45 sec.	0 min. 51 sec.
15	G	72	0.5805	460	1 min. 05 sec.	1 min. 08 sec.	1 min. 02 sec.
16	G	73	0.5792	650	0 min. 45 sec.	1 min. 02 sec.	1 min. 10 sec.
17	G	74	0.5891	510	0 min. 58 sec.	0 min. 48 sec.	0 min. 58 sec.

TABLE NO. 1—CONTINUED

Experiment No.	Manufacturer	Batch No.	Average weight of one tablet in gm. in each Batch	Average resistance (hardness) of 75 tablets in Kgm/sq. c. in each Batch	Test Results: Method A (Swiss Pharmacopoeia) Average time of disintegration	Method B (B. P. 7th Add.) Average time of disintegration	Method C ("artificial stomach") Average time of disintegration
				Mepacrine Hydrochloride 0.1 gm. Tablets			
18	J	91	0.1544	416	1 min. 45 sec.	0 min. 57 sec.	0 hr. 45 m. 20 sec.
19	K	101	0.1546	358	2 min. 00 sec.	1 min. 48 sec.	0 hr. 49 m. 44 sec.
20	K	102	0.1541	330	1 min. 53 sec.	2 min. 22 sec.	1 hr. 05 m. 12 sec.
				Sulfapyridine 0.5 gm. Tablets			
21	A	2	0.6023	530	1 min. 57 sec.	2 min. 45 sec.	5 min. 11 sec.
22	B	11	0.6256	525	2 min. 23 sec.	2 min. 00 sec.	1 min. 48 sec.
23	B	13	0.5440	654	0 min. 57 sec.	0 min. 55 sec.	10 min. 43 sec.
24	B	14	0.5084	666	1 min. 55 sec.	0 min. 53 sec.	6 min. 01 sec.
25	B	21	0.5450	625	2 min. 12 sec.	1 min. 45 sec.	9 min. 30 sec.
26	B	22	0.5324	741	1 min. 57 sec.	1 min. 35 sec.	31 min. 56 sec.
27	B	23	0.5520	650	2 min. 23 sec.	2 min. 00 sec.	17 min. 53 sec.
28	B	24	0.5574	690	2 min. 43 sec.	0 min. 57 sec.	6 min. 31 sec.
29	C	31	0.6126	690	0 min. 35 sec.	0 min. 56 sec.	1 min. 44 sec.
30	D	41	0.6126	612	2 min. 42 sec.	2 min. 45 sec.	11 min. 15 sec.
31	E	51	0.7256	500	2 min. 15 sec.	1 min. 57 sec.	9 min. 48 sec.

In each experiment 75 tablets were tested in each Batch, 25 for each method A, B and C.

Average weight and resistance represent average of 75 tablets.

The times of disintegration given in each method of testing are average times of disintegration of 25 tablets.

TABLE NO. 2

Experiment No.	Manufacturer	Batch No.	Average weight of one tablet in gm. in each Batch	Average resistance (hardness) of one tablet in Kgm/sq. c. in each Batch	Test Results "In Vitro"		
					Method A (Swiss Pharmacopoeia)	Method B (B. P. 7th Add.)	Method C ("artificial stomach")
					Average time of disintegration	Average time of disintegration	Average time of disintegration
1	N	1001	0.597	634	1 min. 15 sec.	2 min. 08 sec.	3 min. 49 sec.
2	N	1002	0.602	628	1 min. 27 sec.	0 min. 57 sec.	4 min. 58 sec.
3	Z	1111	0.826	630	2 min. 32 sec.	3 min. 49 sec.	11 min. 59 sec.
4	M	1201	0.675	673	21 min. 59 sec.	26 min. 37 sec.	50 min. 01 sec.

TABLE NO. 3

TEST RESULTS "IN VIVO"

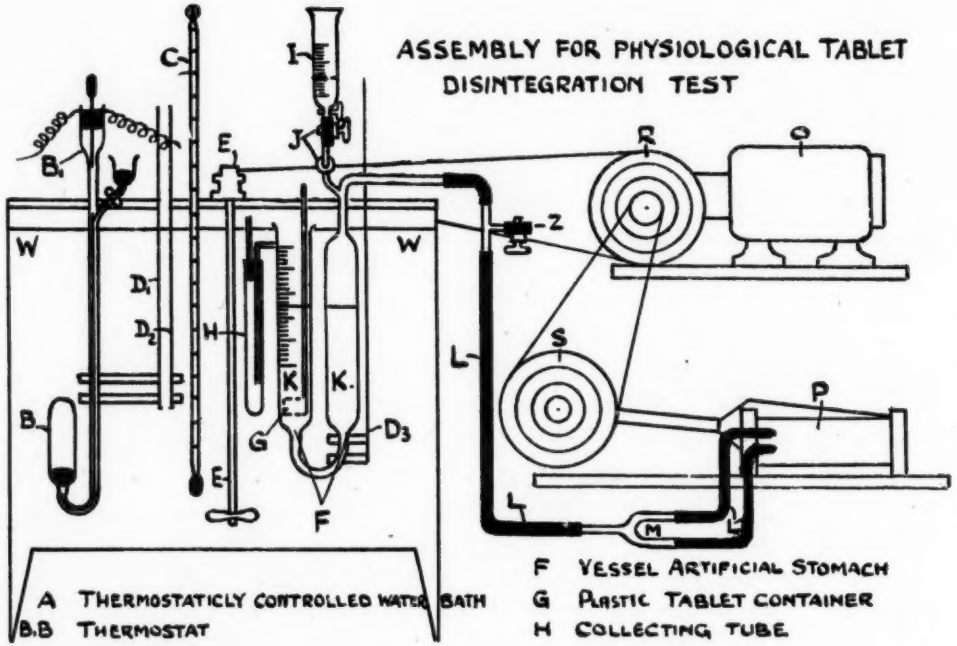
Experiment No.	Manufacturer	Batch No.	Subject "P. S." Average time of disintegration of 5 tablets	Subject "T. C." Average time of disintegration of 5 tablets	Subject "W. M." Average time of disintegration of 5 tablets	Result Average time of disintegration of 15 tablets tested on 3 subjects
1	N	1001	4 min. 52 sec.	3 min. 40 sec.	4 min. 01 sec.	4 min. 11 sec.
2	N	1002	6 min. 32 sec.	4 min. 05 sec.	4 min. 29 sec.	5 min. 02 sec.
3	Z	1111	15 min. 05 sec.	9 min. 58 sec.	10 min. 57 sec.	12 min. 00 sec.
4	M	1201	1 hr. 6 min. 25 sec.	0 hr. 55 min. 33 sec.	0 hr. 58 min. 23 sec.	1 hr. 2 min. 07 sec.

TABLE NO. 4

Experiment No.	Manufacturer	Batch No.	Average weight of one tablet in gm. in each Batch	Average resistance (hardness) of one tablet in Kgm/sq.cm. in each Batch	Test Results: Disintegration test in "Artificial Stomach" — Average disintegration time of 25 tablets without previous saliva bath	Average disintegration time of 25 tablets after 5 sec. bath in human saliva	Average disintegration time of 25 tablets after 15 sec. bath in human saliva	Average disintegration time of 25 tablets after 15 sec. bath in artificial saliva
					Phenobarbiton Gr. ½ Tablets			
1	M	501	0.056	119	7 min. 09 sec.	5 min. 43 sec.	3 min. 58½ sec.	4 min. 01 sec.
					Ephedrine Hydrochloride Gr. 1 Tablets			
2	R	901	0.0854	167	14 min. 47 sec.	11 min. 59½ sec.	11 min. 37 sec.	12 min. 05 sec.
					Sulfathiazole 0.5 gm. Tablets			
3	G	73	0.5792	650	2 min. 21 sec.	1 min. 53 sec.	1 min. 04 sec.	1 min. 10 sec.
4	G	74	0.5891	510	2 min. 05 sec.	1 min. 37 sec.	0 min. 54 sec.	0 min. 58 sec.
					Sulfapyridine 0.5 gm. Tablets			
5	B	23	0.552	650	52 min. 15 sec.	31 min. 22 sec.	17 min. 15 sec.	17 min. 53 sec.
6	B	24	0.5574	690	31 min. 15 sec.	11 min. 20 sec.	6 min. 30 sec.	6 min. 31 sec.
					Mepacrine Hydrochloride 0.1 gm. Tablets			
7	J	91	0.1544	416	1 hr. 29 m. 09 sec.	52 min. 08 sec.	44 min. 53 sec.	45 min. 20 sec.
8	Z	1111	0.826	630	21 min. 01 sec.	14 min. 26 sec.	10 min. 18 sec.	11 min. 59 sec.

TABLE NO. 5

Experiment No.	Manufacturer	Batch No.	Average weight of one tablet in gm. in each Batch	Pressure exerted on the punches (½") in Tons/sq. inch during tableting process. Machine :— Stokes B. 2 in each case	Average resistance (hardness) of one tablet in Kgm/sq.cm. in each Batch & in each case	Average time of disintegration of one tablet in each Batch and in each case using "artificial stomach"
				Sulfanilamide 0.5 gm. Tablets		
1				7.5	480	10 min. 21 sec.
2	L. P.	2002	0.5445	8.1	600	13 min. 07 sec.
3				10.0	650	17 min. 53 sec.
				Sulfanilamide 0.5 gm. Tablets		
4				4.35	200	2 min. 00 sec.
5	L. P.	2003	0.5514	7.5	470	2 min. 35 sec.
6				9.1	600	6 min. 31 sec.
				Sulfadiazine 0.5 gm. Tablets		
7				4.35	270	0 min. 34 sec.
8	L. P.	3001	0.5834	7.5	440	0 min. 45 sec.
9				9.1	510	1 min. 02 sec.



A THERMOSTATICLY CONTROLLED WATER BATH
B.B THERMOSTAT
C THERMOMETER
$D_1D_2D_3$ SUPPORTING RODS AND CLAMPS
E E STIRRER
Z COMPRESSION ADJUSTMENT

F VESSEL ARTIFICIAL STOMACH
G PLASTIC TABLET CONTAINER
H COLLECTING TUBE
I 100c.c. BURETTE
J DROP METER
K ARTIFICIAL STOMACH JUICE-150c.c.
L RUBBER TUBES

M "Y" CANNULA
O ELECTRIC MOTOR (PUMP)
P OSCILLATING RESPIRATION
R ELECTRIC MOTOR WHEEL
S PUMP WHEEL
W WATER LEVEL

FIGURE No. 1

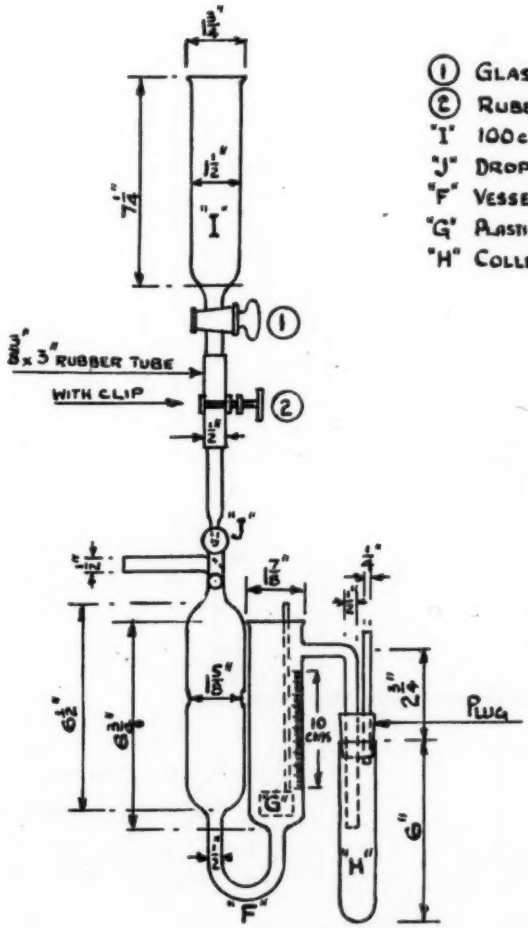

① GLASS COCK
② RUBBER TUBE CLIP
"I" 100 c.c. BURETTE
"J" DROP METER
"F" VESSEL ARTIFICIAL STOMACH
"G" PLASTIC TABLET CONTAINER
"H" COLLECTING TUBE
8mm x 3" RUBBER TUBE
WITH CLIP
7¼"
6½"
6¾"
10 CMS
2½"
PLUG
6"

FIGURE NO. 2

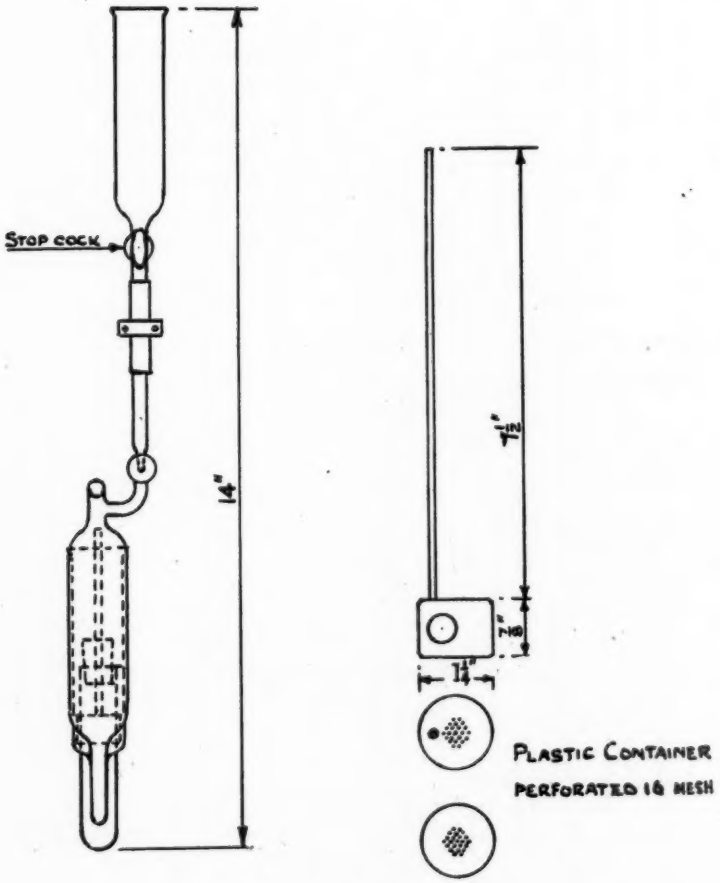
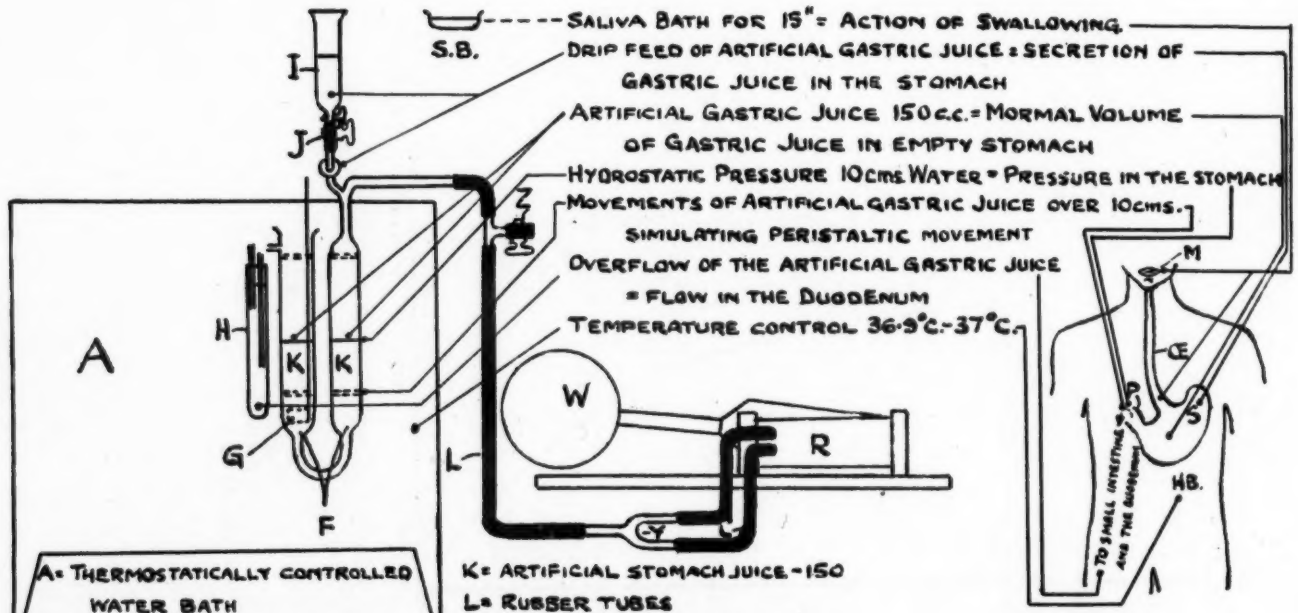


FIGURE No. 3

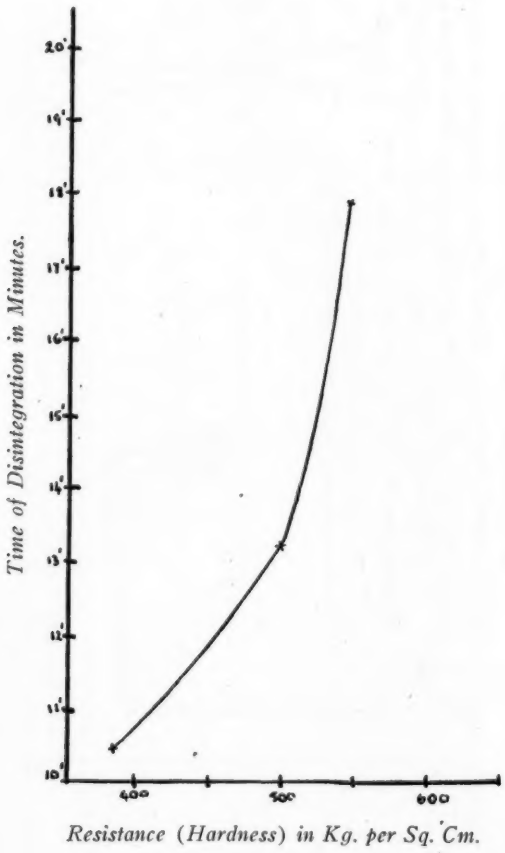


A = THERMOSTATICALLY CONTROLLED WATER BATH
F = VESSEL ARTIFICIAL STOMACH
G = PLASTIC TABLET CONTAINER
H = COLLECTING TUBE
I = 100 C.C. BURETTE
J = DROP ARTIF. GASTRIC JUICE.

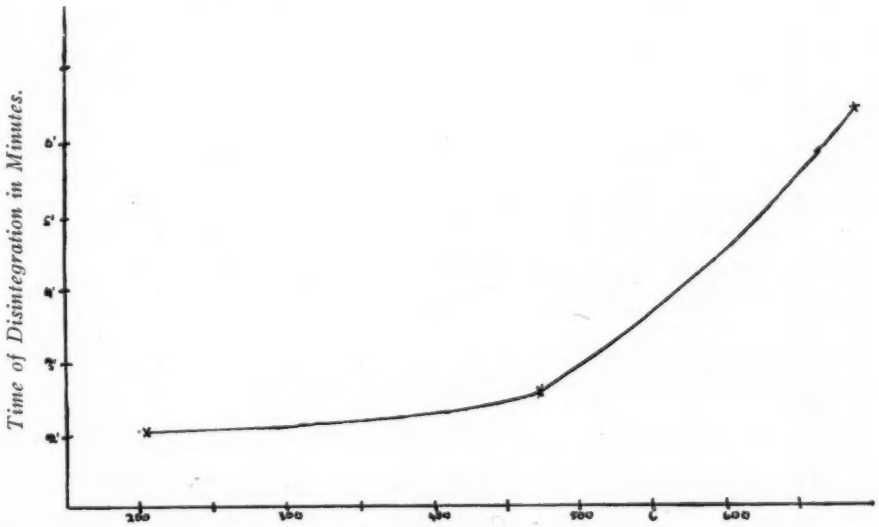
K = ARTIFICIAL STOMACH JUICE - 150
L = RUBBER TUBES
P = OSCILLATING RESPIRATION PUMP
W = PUMP WHEEL
Y = "Y" PIECE
Z = COMPRESSION ADJUSTMENT
SB = SALIVA BATH

M = MOUTH
Œ = OE SOPHAGUS
S = BODY OF STOMACH
P = PYLORUS
H = HUMAN BODY

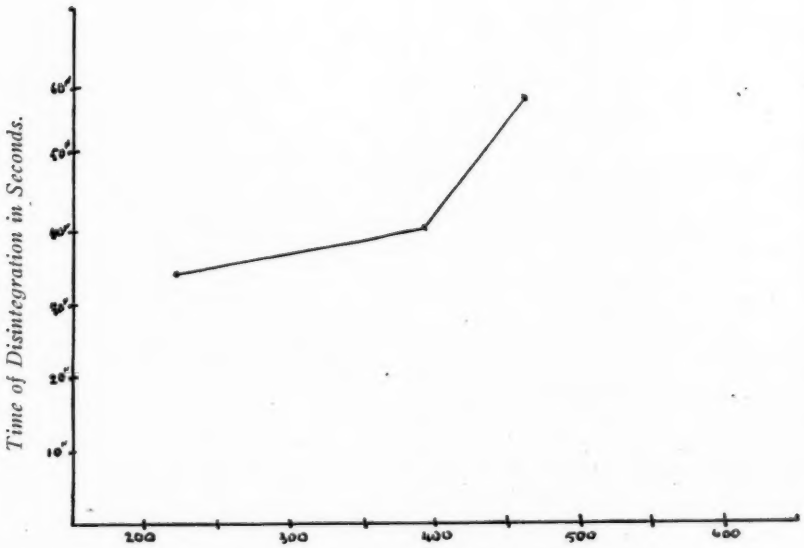
FIGURE No. 4



GRAPH No. 1
Disintegration Curve
Sufanilamide 0.5 gm. Tablets
Manufacturer: L. P., B. No. 2002



GRAPH No. 2
Disintegration Curve
Sufanilamide 0.5 gm. Tablets
Manufacturer: L. P., B. No. 2003



GRAPH No. 3

Disintegration Curve
Sulfadiazine 0.5 gm. Tablets
Manufacturer: L. P., B. No. 3001

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SEROLOGICAL INDICATIONS OF THE SYSTEMATIC RELATIONSHIP OF THE LINGUATULIDA*

By William Ball

Introduction

THE systematic position of the Linguatulida (Pentastomida) has long been a questionable one. A study of some present day texts of zoology and parasitology [Hegner (15), Storer (26), Belding (1), Craig and Faust (8) and Chandler (6)] shows that the Linguatulida are invariably placed as a group at the end of a discussion of the classification of the Arthropoda near the Arachnoidea. In some instances, the Linguatulida are considered to be an order or class of the Arachnoidea; more frequently, they are not given any special systematic status other than being placed in the phylum Arthropoda. The systematic position has been determined by morphological and embryological evidences.

It is the purpose of this paper to offer further evidence or indication of possible relationship by use of the precipitin technique. The value of this immunological technique in animal systematics has been well estabished by Nuttall (23) and later workers (3), (4), (10), (11), (16) and (21).

Historical[1]

Since Von Wrisberg, 1765, (18) first reported his observations of tongue worms, they have been variously placed among the invertebrate phyla (See Table 1). They were placed by Chabert, 1782, (18) in the Cestoda. Humboldt, 1809, (18) considered the tongue worms to be acanthocephalids. The genus *Linguatula,* created by Frohlich, 1789, (18) was placed by Cuvier, 1817, (18) within the class Crustacea next to the wormlike Lernaean copepods which were considered worms at that time. The genus *Pentastomida* was created by Rudolphi, 1819, (18) and was considered by him to be in the class Trematoda, placed between the genera *Poly-*

* Presented to the Faculty of the Philadelphia College of Pharmacy and Science in partial fulfilment of the requirements for the Degree of Master of Science in Biology.

[1] Where the original paper has not been consulted, reference is given to the source of information.

stomum and *Tristomum*. Later Rudolphi raised the Pentastomida to order status. Diesing, 1850, (18) at first considered the tongue worms to be an order with the name Acanthotheca, and intermediate between Trematoda and Nematoda. Later, Diesing, 1856, (7) related them to the Cestoda placing them in the Cephalocotylea. De Blainville, 1828, (24) and Nordmann, 1832, (24) advanced the idea of a relationship between the tongue worms and the Nematoda.

Van Beneden, 1848, (18) (24) (25) was the first to note the arthropod nature of tongue worms classifying them as Crustaceans. The basis of his classification was through study of the morphology and the development of the parasite. The present day conception of the pentastomid relationship to the Acarina originated with Schubaert, 1853, (18) (22). It should be noted that Schubaert (18) also considered that the tongue worms could possibly be related to the Lernaean copepods. Schubaert's (18) views on the arthropod nature of the parasites were further supported by the work of Leuckart, 1860, (22) in his study of the structure and embryology of the tongue worms. Leuckart gave the tongue worms family status calling them the Pentastomidae. He added further evidence of their relationship by his discovery that the cuticle of the tongue worm was chitinous, similar to that of the exoskeleton of the Arthropoda.

The arthropod relationship of the tongue worms was questioned by Lang, 1889, (24) and Pocock, 1897, (24). Von Haeckel, 1896, (13) believed that the tongue worms were related to the Chaetopoda. Ihle, 1899, (20) placed them in a special class of the subphylum Tracheata, phylum Arthropoda. Wineberg (24) claimed a relationship to exist between the tongue worms and Hirudinea.

Sambon, 1922, (24) reviewed the tongue worms as the family Linguatulidae and added evidence to support claims of their acarine nature. Hett, 1924, (17) in a study of the family Linguatulidae briefly discussed the systematics and concurred with the general opinion concerning their arthropod nature. Von Haffner, 1924, (14) considered them as a group related to the annelids.

Heymons, 1935, (18) and Heymons and Vitzthum, 1935, (19) have thoroughly reviewed the status of the tongue worms designating them as a class, the Pentastomida. They have pointed to morphological similarities which exist between the Pentastomida and Annelida and also between the Pentastomida and Arthropoda.

The tongue worms resemble the arthropods in their cuticle, muscular system, coelomic cavity and regression of nephridia. These structures have developed to a different degree and in different ways than those in the arthropods. The tongue worms remain in a much simpler state of organization. The Pentastomida lack a tracheal system and this in itself constitutes a great difference between the Pentastomida and Arthropoda. The tongue worms resemble the annelids in the following: segmentation of the body and body cavity, regression of coelom, presence of parapodia-like structures in certain lower tongue worms, brain and ventral nerve cord, fusion of cephalic segments and the comparison of papillae on the body of the tongue worm to possibly homologous organs on the bodies of annelids. It is the opinion of Heymons (18) based upon the analysis of the similarities listed above that the differences between the Pentastomida and Annelida are of lesser magnitude than those between the Pentastomida and the Arthropoda.

Nuttall, 1904, (23) first extensively applied the precipitin reaction to animal systematics using a flocculation test. The results of 16,000 precipitin tests were published by Nuttall (23) covering a wide portion of animal systematics. Boyden (4) in recent years has established precise and accurate methods of using the precipitin reaction in highly standardized techniques to determine systematic relationships.

In parasitology, immunologic techniques have been applied to the classification, establishment of taxonomic groups and to establish relationship between and within groups of parasites. Culbertson, 1941, (9) has reviewed the work in a number of groups showing the value of various immunologic techniques of which the precipitin reaction is most frequently used.

It is recognized that systematic serology and its evidences do not constitute the only criterion to be used in establishing relationship. Cognizance must be taken of the value of both the morphological and embryological evidences of relationships, and of the fact that discrepancies between morphological and serological relationships may exist. This has been shown in the case of the acanthocephalid, *Macracanthorhynchus hirudinaceus*. This parasite is usually classified with the round worms on the basis of morphology, yet antigenically, it has been shown to be more closely related to the flat worms (11).

TABLE 1

MAJOR RELATIONSHIPS CLAIMED FOR THE LINGUATULIDA

Relationship	*Claimed By*	*Date*
Nematoda	De Blainville (18)	1828
	Nordmann (24)	1832
Cestoda	Chabert (18)	1782
	Diesing (7)	1856
Trematoda	Rudolphi (18)	1819
Acanthocephala	Humboldt (24)	1809
Annelida	Von Haeckel (13)	1896
	Von Haffner (14)	1924
Hirudinea	Wineberg (24)	
Closer to Annelida than Arthropoda	Heymons (18)	1935
Crustacea	Van Beneden (18) (24) (25)	1848
Acarina	Schubaert (18) (22)	1853
	Leuckart (22)	1860
	Sambon (24)	1922

Materials and Methods

Preparation of antigens

As far as possible, fresh materials were used. In some instances it was necessary to use alcohol-fixed or dried material. Helminths were cut into small sections, washed and then ground in a mortar with sand and buffered .85% saline (12). Arthropods and annelids were starved to remove intestinal contents, washed and treated as was the helminth material. Linguatulids in the fresh state were prepared in the same way as the helminths. Alcohol-fixed tongue worms were washed for several hours and then treated the same as the fresh material.

Extraction was accomplished by agitating in buffered .85% saline for one hour. The mixtures were then placed in the refrigerator for 24 hours and shaken intermittantly. At the end of 24 hours, the extraction mass was agitated again and clarified by a preliminary filtering through filter paper, centrifuging for ½ hour at 1800 r.p.m. and a final filtration through a Swinny filter. The Swinny filter was used because of the small amounts of material being filtered. Antigens were stored in the refrigerator (5°C.).

A lipoid-free antigen was prepared by extracting linguatulids ground in a mortar with sand using Bloor's solution [2] in place of saline. At the end of 24 hours, the mass was filtered, washed with Bloor's solution and then extracted with buffered .85% saline for 24 hours, as described in the preceding paragraph in the preparation of antigens. Lipoid-free antigens were used to determine the effect of lipoids on the reaction.

Preparation of the Antiserum

Normal, healthy rabbits were injected with a series of four doubling doses (1cc., 2cc., 4cc. and 8cc.) of Linguatulid antigen on alternate days. When a preliminary bleeding and testing showed weak reactions, a second series of three doses of five cc. each was injected into the same rabbit on alternate days. Blood obtained on a final bleeding (7 days after the last injection) was first clotted; the antiserum obtained by centrifuging was passed through a Swinny filter and stored in the refrigerator.

Method of Testing

Tests were performed using the precipitin, "ring" or interfacial testing technique, in micro test tubes (2). The tubes were made from soft glass tubing, 2.5 mm. in diameter and 60 mm. in length. Antisera and control or negative sera were heated at 56°C for 30 minutes for inactivation. The sera (.05 cc.) were pipetted into the tubes with capillary pipettes and then overlaid with equal amounts of antigens. Tests were incubated at 37°C for 30 minutes and read. Control tests were run with antisera, negative sera, buffered .85% saline and antigen preparations. (See diagram below.)

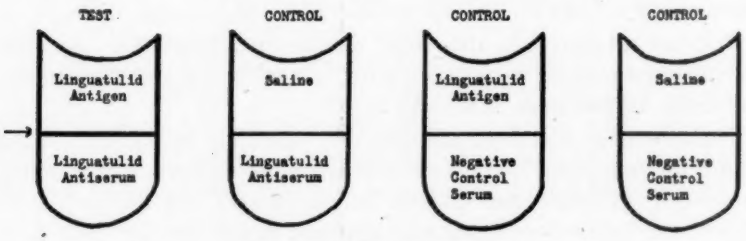


DIAGRAM OF A TEST WITH CONTROLS

The arrow (→) in the photograph above indicates the interface or point at which the ring appears in a positive test.

[2] Three parts absolute ethyl ether, 1 part absolute ethyl alcohol.

Method of Reading

The strength of reaction of undiluted linguatulid antiserum with its homologous (linguatulid) undiluted antigen was designated as plus four (+4), plus three (+3), plus two (+2), plus one (+1), doubtful (±) or negative (—). These values were judged by density, depth, amount of ring and any cloud appearing in the antigen during the test. (See accompanying Table 2 and photograph.)

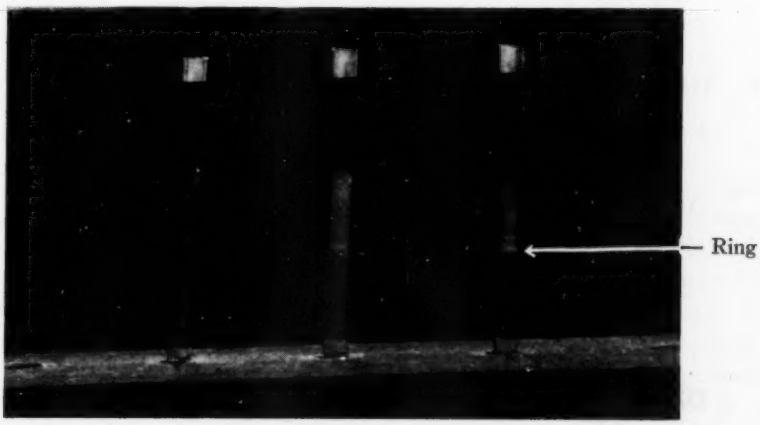
Experimental Results

The results of experiments with helminth, annelid and arthropod antigens using the techniques described previously are summarized in Tables 2, 3 and 4. The results obtained with the lipoid-free testing antigen are given in Table 5.

TABLE 2

TITRATION OF LINGUATULID ANTISERUM WITH HOMOLOGUS ANTIGEN

Dilution of antigen with saline	0	1/1	1/2	1/4	1/8	1/16	1/32	1/64	1/128
[3] 1st injection series (1, 2, 4, 8 cc.	+4	+4	+3	+2	—	—	—	—	—
[4] 2nd injection series (5, 5, 5 cc.	+4	+4	+4	+3	+2	+2	+1	±	—



PHOTOGRAPH OF TESTS

Tube on the left is a negative test; two tubes on the right are positive tests as evidenced by the rings.

[3] Total amount of injected antigen—15 cc.
[4] Total amount of injected antigen—30 cc.

TABLE 3

TESTS OF LINGUALTULID ANTISERUM WITH HELMINTH, ANNELID AND ARTHROPOD ANTIGENS

Antigens	*Test Results*
A. Helminths	
Nematoda	
Ascaris suis	Negative
Cestoda	
Dipylidium canium	Negative
Acanthocephala	
Macracanthorynchus hirudinaceous	Negative
B. Annelids	
Oligochaeta	
Lumbricus sp.	Negative
Polychaeta	
Nereis virens	Negative
Hirudinea	
Hirudo sp.	Negative
C. Arthropods	
Crustacea	
Daphnia pulex	Negative
Arachnoidea	
Araneae	
Aranea sp.	Plus 1 or doubtful
Acarina	
Dermacentor variabilis	Plus three
Diplopoda	
Parajulus sp.	Negative

Of the antigens tested, only the arthropod, *Dermacentor variabilis,* gave a distinct positive reaction.

TABLE 4

TITRATION OF LINGUATULID ANTISERUM WITH *Dermacentor* ANTIGEN COMPARED TO TITRATION OF THE LINGUATULID ANTISERUM WITH ITS HOMOLOGUS ANTIGEN

Dilution of antigen with saline	0	1/1	1/2	1/4	1/8	1/16	1/32	1/64	1/128
Dermacentor antigen	+3	+3	+2	+1	—	—	—	—	—
Linguatulid antigen	+4	+4	+4	+3	+2	+2	+1	—	—

The tests with lipoid-free linguatulid antigen and linguatulid antiserum did not produce reactions as strong as the whole linguatulid antigen and the linguatulid antiserum. (See Table 5.)

TABLE 5

TEST OF LIPOID-FREE LINGUATULID ANTIGEN COMPARED TO WHOLE LINGUATULID ANTIGEN

Antigen	*Reading of Test*
Lipoid-free linguatulid antigen	+1
Whole linguatulid antigen	+4

Discussion

The antigens used in these experiments were not standardized for protein content and, therefore, gave only preliminary indications of relationships—the degree of which has not been established. Further studies utilizing the standardized techniques of Boyden (3) may show these relationships in a different light.

Whole organisms have been used in these experiments because it was not practical to use homologous organs or sera when dealing with small organisms.

An objection might be raised to the use of powdered or alcohol-fixed material. However, this procedure is not without precedence (16) (23) and has been successfully used in many serologic experiments.

Admittedly, the use of a single antigen to represent a taxonomic group is not an entirely reliable practice. It has been proven in many cases that common antigens are not present for numerous groups and classes (9). The tests herein described although using a single antigen as group-representative have been conducted with the purpose of exploratory probing leading to the proper direction for future experiments. The experiments indicate that the class Arachnoidea must be more extensively investigated by serologic tests to determine the relationships of the Linguatulida. Of the antigens tested, only *Dermacentor variabilis* antigen produced a strong reaction. The spider antigen gave a weak or doubtful reaction with linguatulid antiserum. In no case were the reactions of heterologous (other than linguatulid) antigens with linguatulid antiserum stronger than the reaction of homologous antigen and antiserum.

In view of results obtained by other workers using precipitin tests in animal systematics, the results of tests described in this paper furnish indications of the relationship of the Linguatulida. This conclusion is based upon the fact that the serum of an animal immunized with the substance of a particular parasite will react strongest *in vitro* with the immunizing substance (antigen) and less strongly with the substance of related organisms—the strength of the reaction being indicative, other conditions being equal, of the degree of relationship of the organisms.

Summary

1. Serological tests using the precipitin, "ring" or interfacial testing technique were made using various whole helminth, annelid and arthropod antigens against linguatulid (*Porocephalus crotali*) antiserum.

2. Results indicate that a closer relationship may exist between the Linguatulida and the Arachnoidea, particularly the Acarina, than with other groups tested.

3. A further and more critical study must be made of the systematic relationships of the Linguatulida by the precipitin technique to amplify and refine implications of the relationship indicated by the experimental results.

Acknowledgment

Acknowledgment is made to Dr. Martin S. Dunn and Mr. Francis M. White, Biology Department, Philadelphia College of Pharmacy and Science, for their guidance and interest. The author extends his thinks to Dr. Bernard Witlin, Bacteriology Department, Philadelphia College of Pharmacy and Science, for his aid and advice in the performance and reading of serological tests. Acknowledgment is made to Dr. J. T. Self, Department of Zoological Sciences, University of Oklahoma, for his kindness in sending specimens of *Porocephalus crotali.*

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SELECTED ABSTRACTS

Radioactive Phosphorus in the Treatment of Chronic Myelogenous Leukemia. J. H. Lawrence, R. L. Dobson, B. V. A. Low-Beer and B. R. Brown. *J. A. M. A. 136:672* (1948). During recent years the procedure of giving total body irradiation with roentgen rays for the treatment of chronic myelogenous leukemia has gained favor. Recent experiments have shown that when radioactive phosphorus (P32) in the form of sodium mono-hydrogen phosphate was injected into leukemic mice the sites of greatest concentration of the phosphorus atoms were the bone marrow and soft tissues such as lymph nodes, liver and spleen. Thus, here was a means of giving internal irradiation particularly to those areas infiltrated with leukemic cells. Irradiation by this means should be more effective than by total body irradiation since the dose given to normal body tissue would be reduced in proportion to that given to the diseased tissue.

In determining the dose of P32 a number of factors are considered. One microcurie of P32 per Gm. of tissue will give a total of approximately 40 roentgens of radiation in a twenty-four hour period. Although the dose may be expressed in microcuries the roentgen equivalents must be known since past experience has been based upon roentgen equivalents from ray irradiation. The percentage of uptake, the rate of excretion, and the rate of decay of P32 are also factors in the determination of dose. The hematologic response and clinical observation of the patient are the final criterion in the determination of dosage. The doses in general were from 1 to 2 millicuries once or twice a week. A high dose equivalent to 40 millicuries intravenously over a period of 72 days has been given. The dosage must be markedly individualized for there is extreme variation in the response of patients to irradiation.

In this study of 129 patients with chronic myelogenous leukemia treated with P32 irradiation it was found that comfortable life is prolonged. Thirty-three patients lived 5 or more years after the onset of symptoms. Although P32 does not produce any marked improvement in the duration of life in this disease it does provide a convenient method of giving generalized irradiation and it has the added advantage of not producing radiation sickness. P32 is

probably the best therapeutic agent available at the present time for the treatment of this disease, but, the results reported by the author and his associates seem to indicate that the best which can be expected from irradiation therapy is palliation with little or no effect on the ultimate outcome. Thus the authors recommend that other methods for the control of this baffling disease be studied.

Chemical Protection From Poliomyelitis. R. N. Bieter. First International Poliomyelitis Conference, New York, July 1948. Pentnucleotide and yeast nucleic acid were found to protect up to 90 per cent of mice experimentally exposed to "MM" virus, which produces a poliomyelitis-like disease in mice. This discovery was made during experiments with a total of 393 compounds to try to find a substance which would satisfy the demand of the virus for nucleoprotein. The marked specificity of the virus for the cells of the central nervous system, which have a high nucleoprotein content, suggested the possibility of providing other forms of nucleoprotein within the animal in the hope that the virus would utilize this supplementary source and spare the nucleoprotein of the central nervous system of the host.

Yeast nucleic acid was probably the most effective compound tested. The mice were given three injections on days preceding infection and then two doses on the first and third days following infection. Death or paralysis was prevented in 90 per cent of the mice. Pentnucleotide was somewhat less effective, giving protection to 66 per cent of the infected mice.

The nucleic acids showed some curative effects. Nine of 20 infected mice survived without paralysis when nucleic acid injections were given on the first, third, fifth and seventh days following injection of the virus. As a further test of this curative action, a suspension of the virus and nucleic acid was kept in test tubes for two hours and then injected into normal mice. Seventy-five per cent of the mice survived. This suggests that the acid is directly toxic to the virus or else in some way changes the characteristics of the virus to such a degree that it loses its infectiveness.

Other compounds which showed some degree of effectiveness against the virus were pteroylglutamic acid, trypan red, and certain azo dyes.

Iontophoresis With Penicillin Salts. A. J. Pereyra. *U. S. Nav. Med. Bull. 48*:40 (1948). The use of penicillin locally for the treatment of various localized infections of the eye, ear and nasal sinuses, mastoid infections, diseases of the mouth, pyodermas, syphilitic ulcers, etc., has become more prevalent during recent years. In order to try to increase the tissue penetration and absorption of penicillin some investigators have used iontophoresis. However, results have been varied and conflicting. The author conducted experiments to try to clarify the situation.

In vitro experiments proved that sodium and calcium salts of penicillin conduct an electric current and compare favorably with other salts which have been used by iontophoresis.

In vivo experiments revealed that no detectable blood levels of penicillin were obtained following its application by iontophoresis nor by embrocation. However, significant amounts of the antibiotic were recovered from the urine following application by iontophoresis, but no detectable amounts were recovered in the urine following application by embrocation. Iontophoretic application by means of the conventional saturated gauze pad decreased the amount of penicillin recovered in the urine by over 58 per cent as compared with a free aqueous solution in a glass chamber with the solution in direct contact with the skin. The amount of penicillin recovered in the urine varied directly with the concentration of the solution, the duration of treatment, and the strength of the current used.

The author applied these findings to 13 cases of chancroidal ulcers. Administered parenterally penicillin will not cause the remission of these ulcers. However, penicillin by iontophoresis was successful in the treatment of all 13 cases. It is felt that the high local therapeutic concentrations of penicillin, much higher than would be possible from parenteral administration, are responsible for the favorable results.

BOOK REVIEWS

Remington's Practice of Pharmacy (Ninth Edition). By E. Fullerton Cook, P. D., Ph.M., M. Sc., with Eric W. Martin, Ph. C., B. Sc., M. Sc., with more than forty associate editors. Pp. x+1511, including index, with over 800 illustrations. The Mack Publishing Co., Easton, Pa., 1948. Price: $16.00.

"Remington's Practice of Pharmacy" has for many decades been the outstanding text and reference book of pharmacy in the United States. This, the new ninth edition, is indeed a worthy successor to the long list of outstanding earlier editions.

The book is printed on excellent paper with an entirely new format, the pages being 8¼ × 11¼ in size and prepared in double column for easier reading. The arrangement of text follows a similar pattern as in previous editions but much has been done to group the material in the currently accepted categories of modern science. Extensive cross references are used where such are needed to assist the student as well as those using the book as an authoritative reference. A very complete index simplifies greatly the finding of specific information in the shortest possible time.

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Galenicals and Other Pharmaceutical Preparations
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The Pharmacist in Public Health Services
Business Methods of Pharmacy
Hospital Pharmacy
Manufacturing Pharmacy
Biological Products
Perfumery and Cosmetics
Appendix.

The services of over forty acknowledged experts as associate editors, in the prepartion of the text and in the writing of special chapters has done much to make the book authoritative and a completely up-to-date reference. The names of a few of these nationally known specialists and their contribution to the book is evidence of its high calibre. Dr. Joseph Rosin was the Chief Chemical Editor. All the therapeutics throughout were presented by Dr. Louis S. Goodman and his equally famous associate Dr. Alfred Gilman. These outstanding pharmacologists are known the world over for their own standard text on pharmacology. Dr. E. L. Sevringhaus and Dr. Kenneth W. Thompson prepared the chapter on hormones; Dr. Arthur Osol, the sections involving physical chemistry; Dr. Louis Gershenfeld, certain sections dealing with biological products; Dr. O. L. Kline, the chapter on vitamins; Professor Louis Zopf, Ointments; Dr. Curt P. Wimmer, Cosmetics; Dr. E. Emerson Leuallen, Incompatibilities; Dr. Robert P. Herwick, Labels and Labelling; Dr. Robert L. Swain, Pharmaceutical Law; Dr. Paul C. Olsen, Business Administration.

Many other equally renowned specialists contributed chapters on such subjects as Antibiotics, Surface Active Substances, Proteins and Amino-Acids, Blood Fractions, Insecticides, Hospital Pharmacy, Biological Products, Radioactivity, Surgical Supplies, and others.

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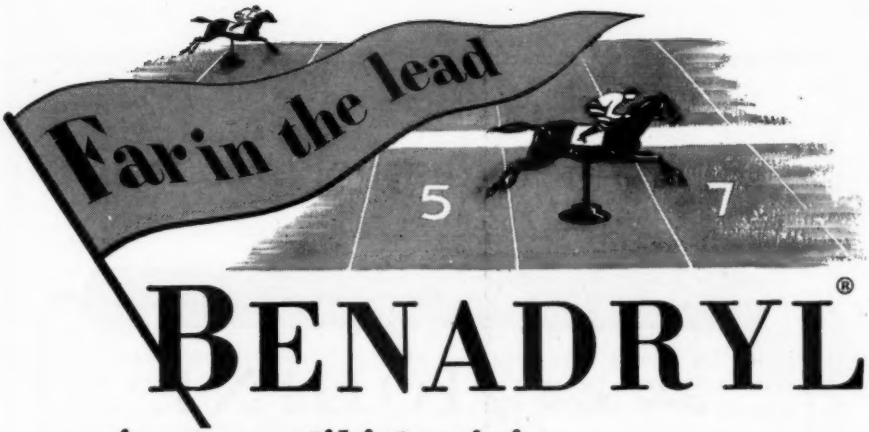

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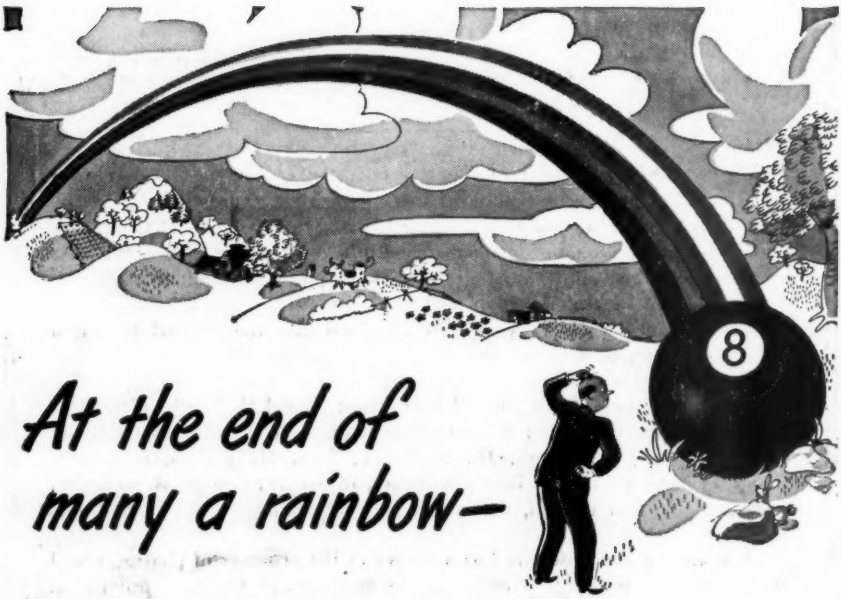

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